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(54) Title: ANTIVIRAL ALKYL SUBSTITUTED PURINE DERIVATIVES AND THEIR PREPARATION

(57) Abstract

The invention relates to a new process for the preparation of alkyl substituted purine derivatives, especially of N7 and N9 alkyl derivatives of purine, and to novel compounds, namely N7 alkyl derivatives of purine endowed with a potential biological, e.g. antiviral or antitumoural activity. This new process enables the regioselective coupling of a specific alkyl group in 7 or 9 position of purine.

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ANTIVIRAL ALKYL SUBSTITUTED PURINE DERIVATIVES AND THEIR PREPARATION

The invention relates to a new process for the preparation of alkyl substituted purine derivatives, especially of N7 and N9 alkyl derivatives of purine, and to novel compounds, namely N7 alkyl derivatives of purine endowed with a potential biological, e.g. antiviral or antitumoural activity. This new process enables the regioselective coupling of a specific alkyl group in 7 or 9 position of purine.

Purine derivatives, in majority substituted in 9 position represent a plurality of important active substances endowed with antiviral activity. *Inter alia*, there are indicated: aciclovir, ganciclovir, and famciclovir and the like, which are still being researched. Recently, promising biological results for N7-substituted 2-amino purine possessing an acyclic component characteristic for ganciclovir (EP-A 448 006, EP-A 452 680), enhanced the palette of interesting active substances. Purine derivatives are usually prepared by coupling the side chain to the basic purine base. The basic problem and challenge are therefore an appropriate choice of the starting base (raw material), enabling the selective introduction of the selected side chain at the desired site, namely the N7 or N9 position.

Regioselective alkylation of guanine is, of course, no trivial problem. At first, the N1 and N3 positions have to be protected or deactivated. The coupling to the N7 position is a kinetically controlled process, whilst the N9 substituted derivatives are thermodynamically more stable. The final ratio between said products is also especially dependent on the substituent in C6 position (Nucleosides & Nucleotides, 8, 225, 1989).

Provided, that owing to economic reasons the choice of the starting substances is concentrated on low-priced naturally obtained derivatives, easily available by industrial fermentation, to say guanosine and *via* said substance guanine, a serious problem is envisaged. Martin *et al.* have as late as 1983 isolated a mixture of N7 and N9 substituted compounds when using diacetyl guanine (J. Med. Chem., 26, 559, 1983). The same applies to the penciclovir synthesis (Chinese J. Chem., 9, 536, 1991).

It should be now mentioned, that the majority of academic work in the search for novel purine derivatives has been performed with 2-amino-6-chloro purine. By various means it was succeeded to enhance the ratio of the yields of individual derivatives N9 : N7 to values as high as 40 : 1. The condensation, however, was not selective. It also should be noted at this occasion, that 2-amino-6-chloro purine represents a high-priced mutagenous compound. (Tetrahedron Lett.; 33, 469, 1992). We intentionally refrained from using it.

Last but not least, there was surprisingly established the outstanding biological activity of purine analogs possessing an acyclic component bound in position N7 (EP-A 448 006, 542 680). This fact is a further incentive in the search for general solutions in the selective coupling to the desired N7 and N9 positions. The first successful results were achieved by means of the N-triacetyl glyoxal derivative of guanine (US Patent 4,701,526; Acta Chem. Scan. B, 41, 564, 1987); they succeeded in the selective binding of the alkyl group to the 7 position, however, with a poor yield (J. Het. Chem. 23, 625, 1986).

For this reason, the very use of alkyl chains in the substitution of purine resulted in the need for a new process.

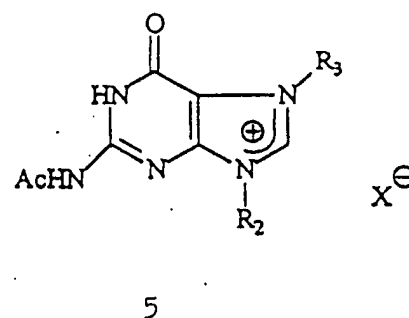
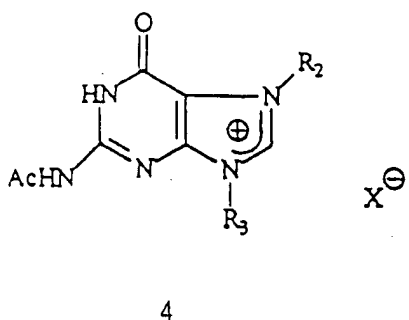
The object of this invention is a new, regioselective process for the preparation of alkyl substituted purine derivatives, specifically N7 or N9 alkyl purine derivatives, starting from 7- or 9- benzyl guanine.

A further object of this invention are N7 alkyl purine derivatives, that are novel compounds endowed with a potential biological, e.g. antiviral or antitumoural activity.

The solution of the above discussed problems, chosen by the present inventors, was the synthesis route characterized by the protection of the imidazole moiety of the guanine molecule possessing a benzyl group in 7 position or in 9 position dependent on the desired site of the substituent binding. The benzyl group may introduced in 7 position *via* the native nucleoside (guanosine) obtained by fermentation in a simple manner. (P. Brookes et al., J. Chem. Soc. (C) 2026, 1968 and P.K. Bridson *et al.*; Synthetic Commun.; 20, 2459, 1990). The protection of a specific site means, of course, the possibility of performing a selective condensation to the remaining active 7 or 9 position.

In the continuation of the reaction, the release of the protecting group located at the second nitrogen atom of the imidazole moiety of the molecule yields the desired compound in a regioselective way. In this manner, we also succeeded in the preparation of 9-benzyl guanine, namely from 7-benzyl guanine; the latter was used for further research. We also disclose a process for the preparation of famciclovir *via* the intermediate penciclovir obtained in conformance with the claimed process starting from 7-benzyl guanine.

According to this invention are obtained compounds of the formula 4 or 5:



wherein:

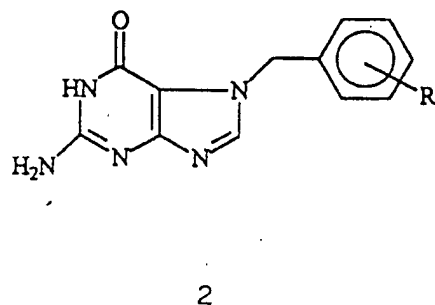
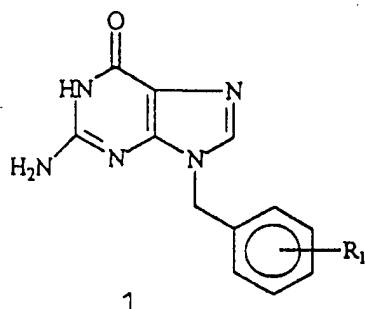
Ac represents acetyl,

R₂ represents a C₁-C₁₂ linear or branched, saturated or unsaturated alkyl group, that may contain a 3-7 membered ring in the molecule, and also an ether, thioether, acetal, thioacetal, lactone, thiolactone, mono- or diacyl group, phosphorylmethoxy, phosphorylethoxy and phosphate groups,

R₃ represents ring substituted p-methoxy, p-nitro, p-methyl benzyl groups,

X represents chloro, bromo, iodo, p-toluene sulphonic groups or mesyloxy groups;

by the reaction of the compound represented by the formula 1 or 2



wherein R₁ represents hydrogen, a C₁-C₆ alkyl group, a C₁-C₁₆ alkoxy group, a hydroxy group, a nitro group, an amino group, fluoro, chloro, bromo or iodo,

with the compound representing the desired substituent (chain) with the reactive removable group, represented by the formula 3

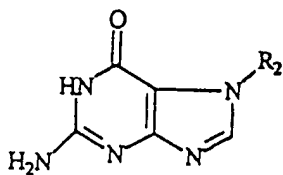


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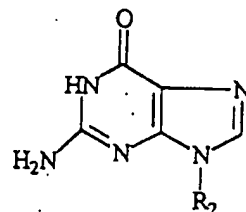
wherein X and R₂ have the above meanings.

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According to this invention are prepared 9- and 7-substituted purine derivatives represented by the formula 6 or 7



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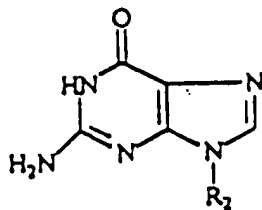


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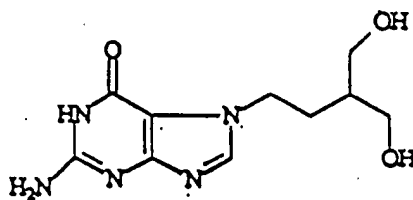
wherein R_2 has the above meanings,

by hydrogenation of the above compounds of formulae 4 and 5.

This invention discloses the preferred example of the synthesis of penciclovir



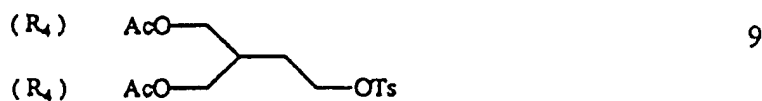
and the N7 isomer thereof represented by the formula 10



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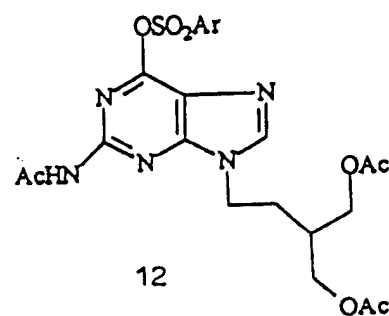
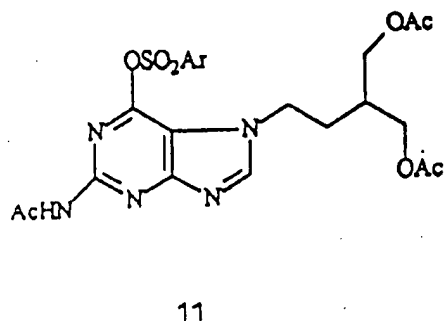
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In the preparation of the above compounds the chain R_2X is represented by the formula 9



wherein R_4 represents a C_1 - C_8 acyl group, a C_1 - C_{10} alkyl group or a C_7 - C_{22} arylalkyl group.

The claimed process comprises the deoxygenation of the compounds of formulae 6 and 7 via the O6-sulphonylated intermediates of formulae 11 and 12

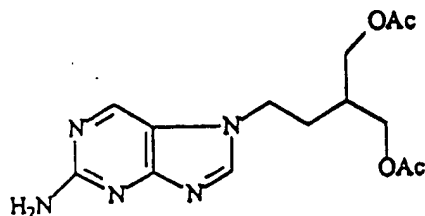


wherein

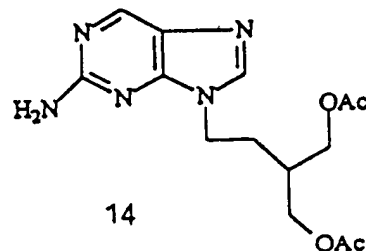
Ac represents acetyl,

Ar represents 2,4,6- i Pr $_3$ C $_6$ H $_2$ -, 2,4,6-Me $_3$ C $_6$ H $_2$ -, 4-MeC $_6$ H $_4$ -, 4-FC $_6$ H $_4$ -,

into the famciclovir of the formula 14 and the isomer thereof of the formula 13



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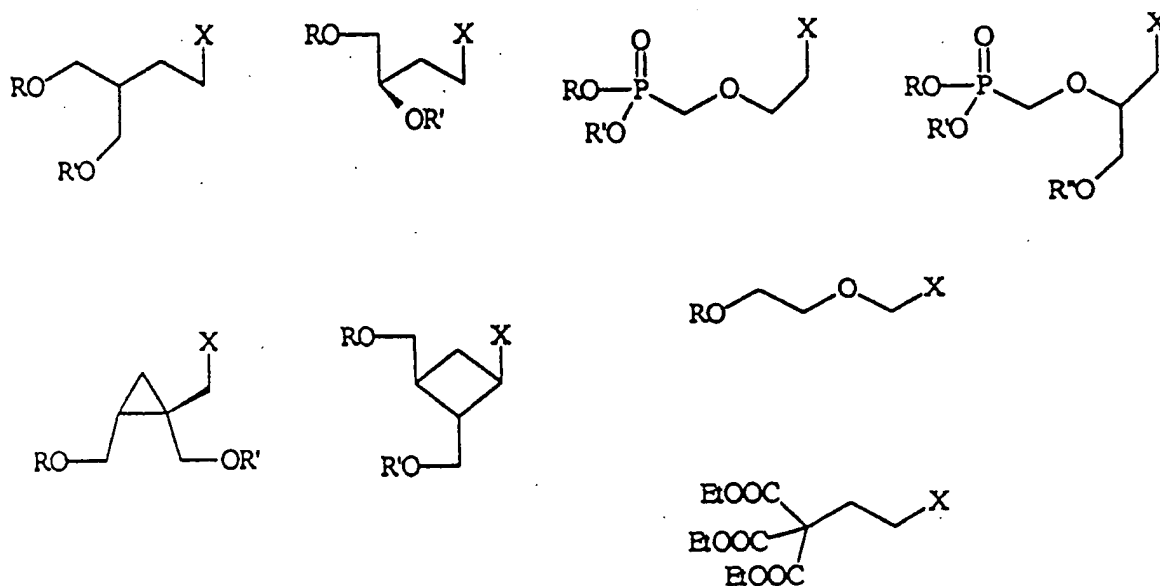
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wherein Ac has the above meaning.

The starting substances used in the claimed process, to say the substituted N7-benzyl derivatives, may be obtained starting from purine nucleosides and the latter converted by hydrogenation *via* the intermediate of the formula 4 (R_3 = benzyl) into 9-benzyl guanine.

The compound of the formula 3 in conformance with this invention possesses a removable group, such as chloro, bromo, iodo, tosyl or mezl groups, in the above mentioned linear or branched chain. In this invention the alkyl group represents a side chain characteristic for potentially bioactive nucleoside active substances, and is bound to the purine ring. The product of this composition has antiviral or antitumoural properties. The reaction is preferably characterized by the following substituents without, however, limiting its scope.

In the following formulae R, R' and R'' represent acetyl, benzoyl, benzyl or other standard protecting groups, and X has the same meanings as mentioned in the description of formulae 4 and 5.



The above mentioned compounds, to say the N-substituted derivatives, are known active substances. On the other hand, the N7-substituted derivatives are novel compounds.

The condensation reaction is performed in organic solvents, such as DMF, DMSO, 1-methyl-2-pyrrolidone, preferably in 1-methyl-2-pyrrolidone and at a temperature of 80 to 120 °C and is terminated within a few hours. The excess of the side chain (20 to 50%) is needed to improve the yield.

The compounds of formulae 4 and 5 are novel compounds, with the exception of the compounds disclosed in EP-A 728757 A.

The compounds of formulae 4 and 5 are obtained according to the above process, usually form salts. In the case, that the salt is not precipitating the debenzylation (hydrogenation) reaction may be performed on the crude product. Upon removal of the benzyl group the desired intermediates 6 and 7 are obtained. Conventional methods may be applied, such as the reduction in the presence of the palladium catalyst under hydrogen, or by means of formic acid or ammonium formate in standard solvents.

In this manner the claimed invention discloses and enables the regioselective preparation of alkylated purine derivatives directly from guanosine possessing substituents in position 9. The 9-substituted derivatives are applicable as medicines. The novel 7-substituted isomers, especially after the deoxygenation into 2-amino-7-alkil compounds represent a novel series of compounds endowed with potential biological activity e.g. an antiviral or an antitumoural activity.

The claim invention is illustrated by the following working Examples, without limiting its scope in any way.

Synthesis Example 1

7-Benzylguanine

Guanosine (56.6 g; 0.2 mole) was suspended in DMSO (150 mL) with stirring. The suspension was stirred for 20 min and then benzyl bromide (13 mL; 0.11 mole) was added. The reaction mixture was stirred at room temperature for 24 hours, and the resulting solution was then transferred to a beaker. 10% HCl (250 mL) was then added, and the mixture heated at 70° C for 2 hours, then cooled and filtered. The crystalline solid was washed with cold water, suspended in water and neutralized by addition of 6 M NaOH. The precipitate was filtered, washed with water and dried *in vacuo* at 120° C to yield 41 g (85%) of 7-benzylguanine in a powder form. This material can be used without further purification: m.p. > 360° C;

¹H NMR (DMSO-d₆) δ 8.07(1H,s,); 7.27-7.36(5H,m); 6.13 (2H,br.s); 5.41 (2H, s).

Synthesis Example 2

N²-Acetyl-7-benzylguanine

7-Benzylguanine (9.65 g; 0.04 mole) was suspended in 1-methyl-2-pyrrolidone (40 mL) and then acetic anhydride (5.7 mL; 0.06 mole) was added. The resulting suspension was heated with stirring at 150° C for 1 hour. The solvent was removed and the residue suspended in ethyl acetate (50 ml) and filtered. The resulting solid was washed with acetone (10 mL) to yield a white powder (10.5; 93%); m.p. 236-238° C;

MS (FAB) m/e = 284 (MH⁺, 100%); UV (H₂O, pH = 6.4) λ_{max} = 266 nm

(ε = 14.500); HRMS for C₁₄H₁₃N₅O₂ calc. 283.107, found 283.107; ¹H NMR (DMSO-d₆) δ 12.11 (1H, br.s), 11.58 (1H,s), 8.35 (1H, s), 7.31-7.35 (5H,m), 5.51 (2H,s), 2.15 (3H,s).

Synthesis Example 3

7,9-Dibenzyl-N²-acetylguaninium bromide

Benzyl bromide (3.3 mL, 0.03 mole) was added to the suspension of N²-acetyl-7-benzylguanine (5.6 g, 0.020 mole) in 1-methyl-2-pyrrolidone. The reaction mixture was heated with stirring at 120° C for 2 hours, then poured still hot into ETA (150 mL) and stirred for 1 hour. The resulting solid was filtered and washed with acetone (10 mL) and after drying yielded 7,9-dibenzyl-N²-acetylguaninium bromide (8.1 g, 90%);

MS (EI) m/e = 373 (M-HBr, 60%), HRMS for C₂₁H₂₀N₅O₂Br-HBr calc. 373.154, found 373.155; ¹H NMR δ 12.61 (1H, br.s), 12.14 (1H, s), 9.83 (1H,s), 7.38-7.52 (10H, m), 5.71 (2H, s) 5.50 (2H, s), 2.22 (3H,s).

Guanine (4.53 g, 0.03 mole) was suspended in 1-methyl-2-pyrrolidone (50 mL), Ac₂O (7.3 mL, 0.07 mole) was added and the reaction mixture stirred for 4 hours at 150° C. The solvent was removed, and fresh 1-methyl-2-pyrrolidone and benzyl bromide (7.2 ml, 0.06 mole) were added subsequently. The reaction mixture was then heated for 2 more hours at 120° C. The dark coloured solution was transferred into hot ETA (250 mL) with stirring . After sufficient cooling of the mixture, salt began to separate, which was after 1 hour period collected on a filter and washed with acetone (2x 25 ml). A slightly coloured salt was obtained after drying *in vacuo*. (12.6 g, 92%). This material was used without further purification.

Synthesis Example 4

9-Benzylguanine

10% Pd/C (1.2 g) was added to a solution containing 7,9-dibenzyl-N²-acetyl guaninium bromide (11.5 g, 0.025 mole) and ammonium formate (4.4 g, 0.07 mole) in methanol (230 ml). The mixture was heated with stirring at reflux for 4 hours, filtered hot and the catalyst washed with hot methanol. Water ammonia (20 mL) was added to the filtrate and the solution heated at reflux for 1 hour. The solvent was removed, and the residue crystallized

from DMF. A mixture of 7- and 9-benzylguanine in a ratio of 1:7 was obtained (determined by NMR) (4.85 g, 80 %). The mixture (0.5 g) was transferred on a filter funnel filled with Celite and washed with MeOH (500-700 mL). The resulting filtrate was concentrated to provide 9-benzylguanine (0.4 g, 91 %):

m.p. $>300^{\circ}\text{C}$, UV (H_2O , pH 6.2) $\lambda_{\text{max}} = 255\text{ nm}$ ($\epsilon = 13300$); MS (FAB) $m/e = 242$ (MH^+ , 60%); HRMS for $\text{C}_{12}\text{H}_{11}\text{N}_5\text{O}$: cal. 241.096, found 241.096; ^1H NMR (DMSO-d_6) δ 10.63 (1H, br.s), (7.76 (1H, s), 7.20-7.37 (5H, m), 6.45 (2H, br.s), 5.18 (2H, s).

Synthesis Example 5

N^2 -Acetyl-9-benzylguanine

Ac_2O (2.9 mL, 0.031 mole) was added to a suspension of 9-benzylguanine (3.7 g, 0.015 mole) in 1-methyl-2-pyrrolidone (25 mL). The reaction mixture was heated at 150°C for 4 hours and the solvent removed. Fresh 1-methyl-2-pyrrolidone was then added, followed by diethylether, with vigorous stirring. The mixture was allowed to cool overnight. The resulting crystals were separated, washed with THF and dried to yield N^2 -acetyl-9-benzylguanine (1.95 g, 46%).

m.p. $=223-226^{\circ}\text{C}$, UV (H_2O , pH $=7.0$) $\lambda_{\text{max}} = 261\text{ nm}$ ($\epsilon = 20900$); MS (FAB) $m/e = 284$ (MH^+ , 100%), HRMS for $\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}_2$ calc. 283.108, found 283.108; ^1H NMR (DMSO-d_6) δ 12.03 (1H, br. s), 11.65 (1H, br.s), 8.09 (1H, s), 7.2-7.3 (5H, m), 5.32 (2H, s), 2.16 (3H, s)

Synthesis Example 6

7-(4-Hydroxy-3(hydroxymethyl)but-1-yl)guanine

N^2 -Acetyl-9-benzylguanine (0.5 g, 1.8 mmole) was suspended in 1-methyl-2-pyrrolidone (5 mL) and 4-acetoxy-3-acetoxymethyl-1-butyl tosylate (0.76 g, 2.1 mmole) was added and heated at 120°C for 2 hours. Then additional 4-acetoxy-3-acetoxymethyl-1-butyl tosylate

(0.28g, 0.8 mmole) was gradually added, and the heating at 120° C continued for 18 hours. The reaction mixture was allowed to cool and then poured into Et₂O (20 mL). One hour later, the solvent was decanted, the residue washed with Et₂O (10 mL) and dissolved in MeOH (25 mL). Char-coal was added and the resulting mixture heated to reflux and filtered hot. Ammonium formate (0.4 g) and 10% Pd/C (0.15 g) were added to the resulting filtrate and the mixture kept at reflux for 4 hours. The mixture was then filtered and the catalyst washed with MeOH (10 mL). The solvent was removed by reduced pressure. The residue was then dissolved in 1 M NaOH (10 ml) and heated on a steam bath for 30 min. The mixture was cooled and neutralized with conc. HCl, allowed to stay for 3 hours until a white solid separated. This solid was filtered, washed with cold water and allowed to dry *in vacuo* at 60° C. White crystals were obtained (132 mg, 29%). ;
m.p. =281-283° C; UV (H₂O, pH =6.5) λ_{\max} = 285 (ϵ =3000); MS (FAB)
m/e =254 (MH⁺, 90%); HRMS for C₁₀H₁₅N₃O₃ calc.253.118, found 253.118;
¹H NMR (DMSO-d₆) δ 10.74 (1H, br.s), 7.93 (1H, s), 6.12 (2H,br.s), 4.41 (2H, br.s), 4.23 (2H, t), 1.74 (2H, m), 1.4 (1H, m).

Synthesis Example 7

9(4-Hydroxy-3-(hydroxymethyl)but-1-yl) guanine

4-Acetoxy-3-acetoxymethyl-1-butyl tosylate (2.15 g, 6 mmole) was added to a suspension of N²-acetyl-7-benzylguanine(1.42 g, 5 mmole) in 1-methyl-2-pyrrolidone (10 mL) and the mixture was heated for 2 hours at 120° C, then repeatedly added further 4-acetoxy-3-acetoxymethyl-1-butyl tosylate (0.36 g, 1 mmol), and reheated at 120° C for additional 2 hours. The reaction mixture was cooled and poured into Et₂O (50 mL). The solvent was decanted after 1 hour period, the residue was washed with Et₂O (10 mL), the solvent decanted again, and the rest dissolved in MeOH (25 mL). Then, char-coal was added, the mixture was heated to boil and filtered hot. Ammonium formate (0.9 g) and 10% Pd/C (0.3 g) were added to the filtrate and the reaction mixture was heated at reflux for 4 hours, then filtered and the remaining catalyst was washed with MeOH (10 mL). The solvent was

removed under reduced pressure and the residue dissolved in 1 M NaOH solution (10 mL) and heated on a steam bath for 30 min. The reaction mixture was allowed to cool and was neutralized with conc. HCl, and then allowed to stand for 3 hours until white crystals began to separate. The solid was collected on a filter, washed with cold water and finally dried *in vacuo* at 60° C. White crystals were collected (0.6 g, 47%);

m.p. = 271-273° C; UV (H₂O, pH = 5.7) λ_{max} = 253 (ϵ = 9100); MS (FAB) m/e = 254 (MH⁺, 62%), 185 (100%); ¹H NMR (DMSO-d₆) δ 10.51 (1H, br.s), 7.68 (1H, s), 6.41 (2H, br.s), 4.44 (2H, br.s), 3.99 (2H, t) 1.70 (2H, m), 1.45 (1H, m).

Synthesis Example 8

N²-Acetyl-9-(4-acetoxy-3-(acetoxymethyl)but-1-yl)guanine

In a suspension of 9-(4-hydroxy-3-(hydroxymethyl)but-1-yl)guanine (1.4 g, 6 mmole) in 1-methyl-2-pyrrolidone (10 mL) Ac₂O (2.4 mL, 25 mmol) was added and the reaction mixture was heated at 150° C for 5 hours. The solvent was removed under reduced pressure and the residue was dissolved in a water-MeOH 50 : 50 mixture, char-coal was added and filtered while hot. The filtrate was allowed to cool in a refrigerator for 2 hours. The separated crystals were filtered and dried to afford N²-acetyl-9-(4-hydroxy-3-hydroxymethyl)but-1-yl)guanine (1.65g + 0.1 g from the second crop g, 83%);

m.p. = 222-223 °C; ¹H NMR (DMSO-d₆) δ 12.02 (1H, br.s), 11.70 (1H, br.s), 8.03 (1H, s), 4.17 (2H, t), 4.03 (4H, d), 2.20 3H,s,), 1.84-2.02 (9H, m).

Synthesis Example 9

9-(4-acetoxy-3-(acetoxymethyl)but-1-yl)-2-acetyl-amino-6-(2',4',6'-triisopropylbenzenesulfonyloxy)9H-purine

A mixture of N²-acetyl-9-(4-acetoxy-3-acetoxymethylbut-1-yl)guanine (1.3 g, 3.4 mmole), 4-dimethylaminopyridine (0.012 g, 1.7 mmole), triethylamine (1.9 mL , 1.4 mmol),

anhydrous dichloromethane (35 mL) and 2,4,6-triisopropylbenzenesulfonyloxy chloride (2.08 g, 6.9 mmol) was stirred at room temperature up to a clear solution (2.5 hours). The solvent was removed and the product was isolated after purification by flash chromatography method (column prepared in CH₂Cl₂, eluted with ETA). A yellow foam was obtained (2.21 g, 99%). and was used in subsequent reactions.

MS (FAB) m/e = 646 (MH⁺, 100%); ¹H NMR (CDCl₃) 8.13 (1H, b.s.), 8.02 (1H, s), 7.25 (2H, s), 4.25-4.11 (8H, m), 2.95 (1H, m), 2.37 (3H, s), 2.14-1.98 (9H, m), 1.28 (18H, d)

Synthesis Example 10

9-(4-Hydroxy-3- (hydroxymethyl)-but-1-yl)-2-aminopurine

9-(4-Hydroxy-3-(hydroxymethyl)but-1-yl)-2-acetylamino-6-(2',4',6',-triisopropylbenzenesulfonyloxy)9H-purine (8.5 g, 13.2 mmole) was dissolved in ethanol (140 mL) , catalyst 10% Pd/C (1.4 g) and triethylamine (19.8 mL), 0.14 mole) were added and the mixture subjected to hydrogenation in a Parr hydrogenator at 80-85° C (3 bar) for 8 hours. The catalyst was filtered off and washed with hot ethanol. An acetylated intermediate (3.1 g, 60%) separated first after cooling the solution. It was dissolved (2.65 g) in water (20 mL) and in aqueous methylamine (40% , 9 mL). The resulting solution was then stirred for 15 min at room temperature, and evaporated and repeatedly co-evaporated with each 10 mL of water. The residue was recrystallized from ethanol to yield 9-(4-hydroxy-3-hydroxymethyl)but-1-yl)-2-aminopurine (1.7 g, 99%).

¹H NMR (DMSO-d₆) δ 8.55 (1H, s), 8.07 (1H, s), 6.49 (2H, s), 4.44 (2H, t), 4.11 (2H, t) , 3.1-3.5 (4H, m), 1.76 (2H, q), 1.45 (1H, m).

Synthesis Example 119-(4-Acetoxy-3-acetoxymethyl)but-1-yl)-2-aminopurine

A mixture of 9-(4-hydroxy-3-hydroxymethyl)but-1-yl)-2-aminopurine (1.75 g, 7.4 mmole), Ac₂O (1.7 mL) in pyridine (1.8 mL), DMAP (90 mg, 7.4 mmole) in anhydrous THF (30 mL) was stirred for 3 hours at room temperature. The solvent was evaporated and the residue dissolved in water. This mixture was extracted with CH₂Cl₂ (3x 40 mL). The organic layer was dried over Na₂SO₄ and the solvent evaporated. A white powder was isolated after the elaboration of the mixture with Et₂O and with subsequent filtration to provide famciclovir (2.3 g, 97%).

¹H NMR (DMSO-d₆) δ 8.56 (1H, s), 8.9 (1H, s), 6.49 (2H, s), 4.13 (2H, t), 4.02 (4H, d), 1.99 (6H, s), 1.87 (3H, m).

Synthesis Example 12N²-Acetyl-7-benzyl-(4-acetoxybut-1-yl)guaninium bromide

4-Bromobut-1-yl acetate (10.7 g, 0.055 mole) was added to a suspension of N²-acetyl-7-benzylguanine (14.1 g, 0.05 mole) in 1-methyl-2-pyrrolidone (35 mL). The reaction mixture was heated for 2 hours at 120° C. The mixture was then cooled down and 500 mL of ETA was added. The precipitate was collected by filtration after 1 hour period, the obtained white salt was washed with acetone and dried to obtain N²-acetyl-7-benzyl-9-(4-acetoxybut-1-yl)guaninium bromide (21 g, 88%), which was used without further purification.

¹H NMR (DMSO-d₆) δ 12.60 (1H, br.s), 12.17 (1H, s), 9.83 (1H, s), 7.4-7.5 (5H, m), 5.72 (2H, s), 4.29 (2H, t), 4.04 (2H, t), 2.23 (3H, s), 2.01 (3H, s), 1.85 (2H, m), 1.67 (2H, m).

Example 139-(4-Acetoxybut-1-yl)guanine

A mixture of N²-acetyl-7-benzyl-9-(4-acetoxybut-yl)guaninium bromide (21 g, 0.044 mole), ammonium formate (7 g, 0.11 mole) in methanol (400 mL) and 10% Pd/C (2.7 g) was heated at reflux for 4 hours, then filtered hot and the remaining catalyst was washed with hot water (50 mL). The filtrate was heated at reflux for an additional hour, then evaporated at reduced pressure, and the residue was crystallized from water to afford pure 9-(4-acetoxybut-1-yl)guanine (7.7 g, 66%). m.p. = 215-216 °C; ¹H NMR (DMSO-d₆) δ 10.54 (1H, s), 7.70 (1H, s), 6.44 (2H, br.s), 3.97 (4H, m), 1.99 (3H, s), 1.77 (2H, m), 1.52 (2H, m).

Synthesis Example 14N²-Acetyl-9-(4-acetoxybut-1-yl) guanine

To a suspension of 9-(4-acetoxybut-1-yl) guanine (3.0 g, 0.01 mole) in 1-methyl-2-pyrrolidone (10 mL), Ac₂O (2.1 mL, 0.02 mole) was added and the mixture was heated at reflux for 5 hours. The reaction mixture was cooled and concentrated to approximately 8 mL of volume. Et₂O (50 mL) was added with stirring, then cooled and the resulting crystals collected on a filter and washed with Et₂O. After drying, N²-acetyl-9-(4-acetoxybut-1-yl)guanine (3.16 g, 91%) was obtained. and could be used in subsequent steps without further purification.; m.p. = 215-218° C; MS (ES) m/e = 307 (M⁺, 100%); ¹H NMR (DMSO-d₆) δ 12.03 (1H, br.s), 11.71 (1H, br.s), 8.01 (1H, s), 4.09 (2H, t), 4.01 (2H, t), 2.18 (3H, s), 2.00 (3H, s), 1.83 (2H, m), 1.55 (2H, m).

Example 15N²-Acetyl-9-benzyl-7-(4-acetoxybut-1-yl)guaninium bromide

4-Bromobut-1-yl acetate (2.9 g, 0.015 mole) was added to 9-benzylguanine (2.4 g, 0.01 mole) in 1-methyl-2-pyrrolidone (20 mL). The suspension was heated at 120° C for 2 hours. Et₂O (200 mL) was added to the cooled solution. After a while (1 hour), the solvent mixture was decanted from a dark coloured gummy residue, which was further elaborated with ETA to provide a salt. This solid was then filtered and washed with ETA. After drying, N²-acetyl-9-benzyl-7-(4-acetoxybut-1-yl) guaninium bromide (4.3 g, 99%) was obtained and it was used in following experiments without further purification. ¹H NMR (DMS)-d₆ δ 11.70 (1H, s), 9.44 (1H, s), 7.41 (5H, m), 7.25 (2H, br.s), 5.38 (2H, s), 4.40 (2H, t), 4.02 (2H, t), 1.90 (2H, m), 1.62 (2H, m).

Example 167-(4-Acetoxybut-1-yl) guanine

A mixture of 9-benzyl-7-(4-acetoxybut-1-yl) guaninium bromide (4.3 g, 0.01 mole), ammonium formate (1.9 g, 0.03 mole), and Pd/C (0.4 g) in methanol (80 mL) was heated at reflux with stirring for 4 hours, then filtered hot, and the filtrate evaporated to dryness under reduced pressure. The catalyst was washed with hot 2 M NaOH solution (30 mL) and this solution was added to the residue. The mixture was then heated on a steam bath for 20 min and neutralized with conc. HCl. After 1 hour, the formed crystals were collected and washed with water, and thoroughly dried to yield : 7-(4-acetoxybut-1-yl)guanine (1.55 g, 71%). ; ¹H NMR (DMSO-d₆) δ 10.76 (1H, br.s), 7.91 (1H, s), 6.12 (2H, br.s), 4.44 (1H, t), 4.18 (2H, t), 3.37 (2H, t), 1.99 (3H, s), 1.78 (2H, m), 1.35 (2H, m).

Synthesis Example 17N²-Acetyl-7-(4-acetoxybut-1-yl)guanine

7-(4-Acetoxybut-1-yl)guanine (1 g, 4 mmole) was acetylated in a suspension of 1-methyl-2-pyrrolidone (10 mL), after the addition of Ac₂O (1.1 mL, 11 mmole) and heating at reflux for 10 hours. The solvent was removed at reduced pressure, the was treated with ETA (5 mL) and the solid separated by filtration. Solid was then washed with acetone and dried to provide N²-acetyl-7-(4-acetoxybut-1-yl)guanine (1.05 g, 90%); MS (ES) m/e = 307 (M⁺, 100%) ¹H NMR (DMSO-d₆) δ 12.05 (1H, br.s), 11.58 (1H, br.s), 8.19 (1H, s), 4.30 (2H, t), 4.00 (2H, t), 2.16 (3H, s), 1.98 (3H, m), 1.51 (2H, m).

Example 187-(4-Acetoxybut-1-yl)-2-acetamino-6-(2',4',6'-triisopropylbenzenesulfonyloxy)-7H-purine

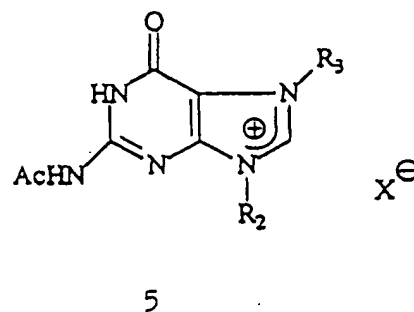
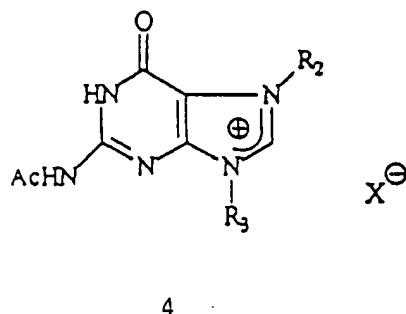
A mixture of N²-acetyl-7-(4-acetoxybut-1-yl)guanine (0.5 g, 1.6 mmole), triethylamine, (0.9 mL), 6.4 mmol) and 4-dimethylaminopyridine (10 mg, 0.1mmoles in anhydrous CH₂Cl₂ (20 mL) and 2',4',6'-triisopropylbenzenesulfonyl chloride (1 g, 3.3 mmole) was stirred at room temperature until the solution cleared up. The solution was washed 2 times with each 15 mL portion of water. The water phase was then washed with 20 mL CH₂Cl₂. The joint organic phases were washed with brine (2x25 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure, the product isolated by "flash" chromatography and processed. (CH₂Cl₂-300 mL; ETA-600 mL), to obtain 7-(4-acetoxy-1-yl-2-acetyl-amino-6-(2',4',6'-triisopropylbenzenesulfonyloxy)7H-purine. (0.9g, 96%) as a yellow foam.; ¹H NMR (DMSO-d₆) δ 8.14 (1H, s), 7.62 (1H, s), 7.27 (2H, s), 4.42 (2H, t), 4.14 (2H, t), 4.06 (2H, m), 2.97 (1H, m), 2.12 (3H, s), 2.07 (3H, s), 1.73 (2H, m), 1.63 (2H, m) 1.30 (6H, d), 25 (12H, d).

Synthesis Example 197-(4-Acetylbut-1-yl)-2-acetylamino-7H-purine

7-(4-acetoxybut-1-yl)-2-acetylamino-6-(2',4',6'-triisopropylbenzenesulfonyloxy)7H-purine (0.55 g, 1 mmole) was dissolved in ethanol (25 mL), then were added 10% Pd/C (0.2 g) and triethylamine (0.15 mL, 1.1 mmole). Hydrogenation was performed in a Parr hydrogenation apparatus at 75° C and 3 bar pressure. After 6 hours, the catalyst was removed by filtration and washed with hot ethanol. A mixture of N²-acetyl-7-(4-acetoxybut-1-yl)guanine and 7-(4-acetoxybut-1-yl)-2-acetylamino-7H-purine was obtained. The products were separated by flash chromatography (CH₂Cl₂ : MeOH = 20:1; 400 mL ; and 10:1, 400 ml) to obtain 7-(4-acetoxybut-1-yl)-2-acetylamino-7H-purine (0.14 g, 50%) as a white solid. ¹H NMR (DMSO-d₆) δ 10.42 (1H, br. s), 9.10 (1H, s), 8.62 (1H, s), 4.35 (2H, t), 4.01 (2H, t), 2.18 (3H, s), 1.98 (3H, s), 1.89 (2H, m), 1.54 (2H, m).

PATENT CLAIMS

1. A process for preparing compounds of the formula 4 or 5:



wherein:

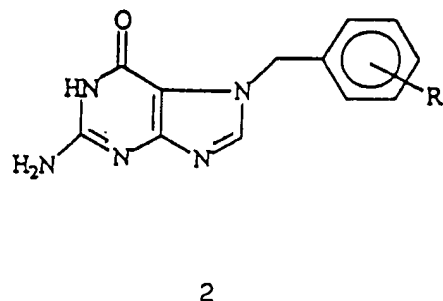
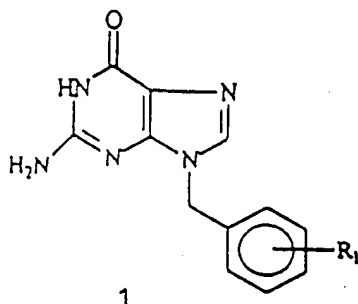
Ac represents acetyl,

R₂ represents a C₁-C₁₂ linear or branched, saturated or unsaturated alkyl group, that may contain a 3-7 membered ring in the molecule, and also an ether, thioether, acetal, thioacetal, lactone, thiolactone, mono- or diacyl group, phosphorylmethoxy, phosphorylethoxy and phosphate groups,

R₃ represents ring substituted p-methoxy, p-nitro, p-methyl benzyl groups,

X represents chloro, bromo, iodo, p-toluene sulphonic groups or mesyloxy groups;

characterized in, that a compound represented by the formula 1 or 2



wherein R₁ represents hydrogen, a C₁-C₆ alkyl group, a C₁-C₁₆ alkoxy group, a hydroxy group, a nitro group, an amino group, fluoro, chloro, bromo or iodo,

22

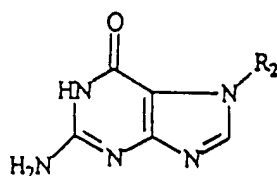
is reacted with the compound representing the desired substituent (chain) with the reactive removable group, represented by the formula 3



3

wherein X and R_2 have the above meanings.

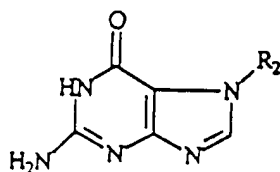
2. A compound of the formula 6



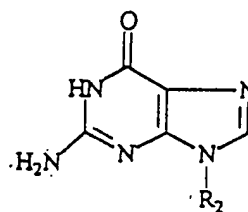
6

wherein R_2 has the meaning defined in claim 1.

3. A process for preparing 9 and 7 substituted purine derivatives of formulae 6 and 7



6

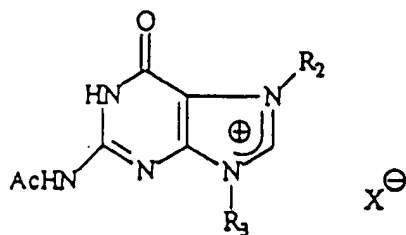


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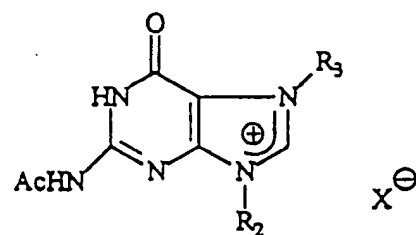
wherein R_2 has the above meanings,

by hydrogenation of the above compounds of formulae 4 and 5.

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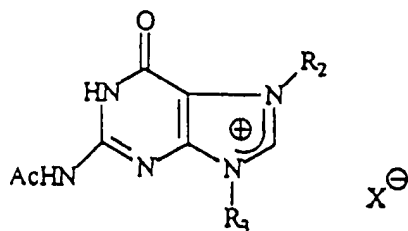
4



5

wherein Ac, X, R₂ and R₃ have the meanings defined in claim 1.

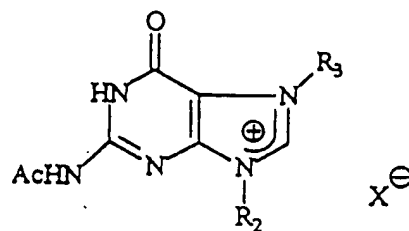
4. Compounds of formula 4



4

wherein Ac, X, R₂ and R₃ have the meanings defined in claim 1.

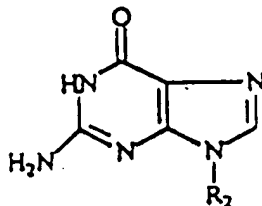
5. Compounds of formula 5



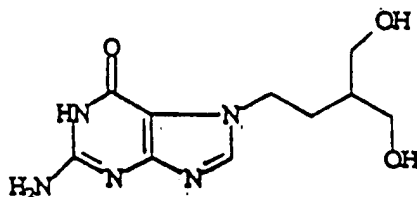
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wherein Ac, X, R₂ and R₃ have the meanings defined in claim 1.

6. A process as claimed in claim 3, characterized in, that it yields penciclovir of the formula

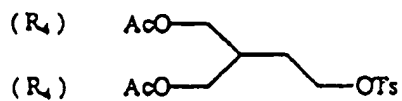


and the N7 isomer thereof represented by the formula 10



10

7. A process as claimed in claim 1, 3, 6, characterized in, that the chain R_2X is represented by the formula 9

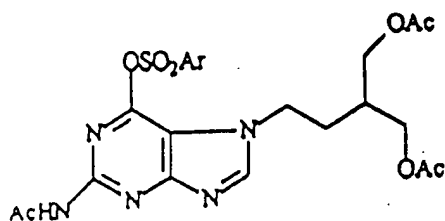


9

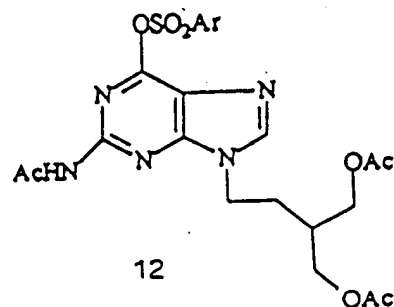
wherein R_4 represents a C_1 - C_8 acyl group, a C_1 - C_{10} alkyl group or a C_7 - C_{22} arylalkyl group.

25

8. A process for the deoxygenation of the compounds of formulae 6 and 7, defined in claim 3, characterized in, that it is performed *via* the O6-sulfonylated intermediates 11 and 12



11



12

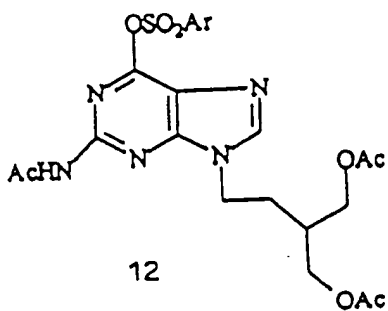
wherein

Ac represents acetyl,

Ar represents 2,4,6- i -Pr₃C₆H₂-, 2,4,6-Me₃C₆H₂-, 4-MeC₆H₄-, 4-FC₆H₄-,

into the famciclovir of the formula 14 and the isomer thereof of the formula 13

9. Compounds of formula 12



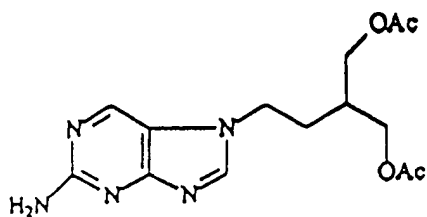
12

wherein Ac has the meaning defined in claim 1, Ar has the meaning defined in claim 8.

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10. A compound of formula 13

{7-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-amino-7H-purine}



13

wherein Ac has the meaning defined in claim 1.

INTERNATIONAL SEARCH REPORT

Inter. nat. Application No

PCT/SI 99/00021

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D473/00 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	the whole document	1,4,5
Y	KJELLBERG J ET AL: "STUDIES ON THE ALKYLATION OF DERIVATIVES OF GUANINE" NUCLEOSIDES & NUCLEOTIDES, XX, XX, vol. 8, no. 2, page 225-256 XP000616145 ISSN: 0732-8311 cited in the application	1-5
	the whole document	

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

22 December 1999

Date of mailing of the international search report

21/01/2000

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/SI 99/00021

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	EP 0 182 024 A (BEECHAM GROUP PLC) 28 May 1986 (1986-05-28) the whole document ---	1-10
X	GEEN,G.R. ET AL.: "Regiospecific Michael Additions with 2-Amino-purines " TETRAHEDRON LETT., vol. 33, no. 32, 1992, pages 4609-4612, XP002126148 OXFORD * see page 4611, ex.9 * the whole document ---	9
X	GEEN,G.A. ET AL.: "The effect of the C-6 substituent on the Regioselectivity of N-Alkylation of 2-aminopurines " TETRAHEDRON, vol. 46, no. 19, 1990, pages 6903-6914, XP002126578 OXFORD the whole document ---	10
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Interr. J. Appl. Application No
PCT/SI 99/00021

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
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P, X	BRAND, B. ET AL.: "Convenient Synthesis of 9-(4-Hydroxy-3-(hydroxymethyl)butyl)-guanine (penciclovir) and 9-(4-Acetoxy-3-(acetoxymethyl)butyl)-2-amino-9H-purine (Famciclovir)" TETRAHEDRON, vol. 55, 1999, pages 5239-5252, XP002126581 OXFORD the whole document -----	1-10



INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

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